Corynebacterium species rarely cause orthopedic infections

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Abstract: Corynebacterium spp. are rarely considered as pathogens but data in orthopedic infections are sparse. Therefore, we asked how often Corynebacterium spp. caused an infection in a defined cohort of orthopedic patients with a positive culture. In addition, we aimed to determine the species variety and susceptibility of isolated strains in regards to potential treatment strategies. Between 2006 and 2015, we retrospectively assessed all Corynebacterium sp. bone and joint cultures from an orthopedic ward. The isolates were considered as relevant indicating an infection if the same Corynebacterium sp. was present in at least two samples. We found 97 orthopedic cases with isolation of Corynebacterium spp. (128 positive samples), mainly Corynebacterium tuberculostearicum (n=26), Corynebacterium amycolatum (n=17), Corynebacterium striatum (n=13), and Corynebacterium afermentans (n=11). Compared to a cohort of positive blood cultures, we found significantly more C. striatum and C. tuberculostearicum but no C. jeikeium cases. Only 16 cases out 66 cases (24.2%) with an available diagnostic set of at least 2 samples had an infection. Antibiotic susceptibility testing (AST) of different antibiotics showed various susceptibility results except for vancomycin and linezolid with a 100% susceptibility rate. Rates of susceptibility of corynebacteria isolated from orthopedic samples and of isolates from blood cultures were comparable. In conclusion, our study results confirmed that Corynebacterium sp. is most often isolated as a contaminant in a cohort of orthopedic patients. AST is necessary to define the optimal treatment in orthopedic infections.

DOI: https://doi.org/10.1128/JCM.01200-18

JCM Accepted Manuscript Posted Online 10 October 2018
J. Clin. Microbiol. doi:10.1128/JCM.01200-18

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Running Head: *Corynebacterium* species in orthopedic infections

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ABSTRACT

Corynebacterium spp. are rarely considered as pathogens but data in orthopedic infections are sparse. Therefore, we asked how often *Corynebacterium* spp. caused an infection in a defined cohort of orthopedic patients with a positive culture. In addition, we aimed to determine the species variety and susceptibility of isolated strains in regards to potential treatment strategies. Between 2006 and 2015, we retrospectively assessed all *Corynebacterium* sp. bone and joint cultures from an orthopedic ward. The isolates were considered as relevant indicating an infection if the same *Corynebacterium* sp. was present in at least two samples. We found 97 orthopedic cases with isolation of *Corynebacterium* spp. (128 positive samples), mainly *Corynebacterium tuberculostearicum* (n=26), *Corynebacterium amycolatum* (n=17), *Corynebacterium striatum* (n=13), and *Corynebacterium afermentans* (n=11). Compared to a cohort of positive blood cultures, we found significantly more *C. striatum* and *C. tuberculostearicum* but no *C. jeikeium* cases. Only 16 cases out 66 cases (24.2%) with an available diagnostic set of at least 2 samples had an infection. Antibiotic susceptibility testing (AST) of different antibiotics showed various susceptibility results except for vancomycin and linezolid with a 100% susceptibility rate. Rates of susceptibility of corynebacteria isolated from orthopedic samples and of isolates from blood cultures were comparable. In conclusion, our study results confirmed that *Corynebacterium* sp. is most often isolated as a contaminant in a cohort of orthopedic patients. AST is necessary to define the optimal treatment in orthopedic infections.

INTRODUCTION

Orthopedic infections, including septic arthritis of a native joint, periprosthetic joint infections (PJI), and osteomyelitis, are typically treated in specialized orthopedic centers. Most of these infections are chronic, and they are difficult to diagnose and to treat due to biofilm formation (1). A definitive criterion for orthopedic infections is growth of the same pathogen in at least two diagnostic samples or presence of a sinus tract in implant-associated infections (2, 3). The significance of a single positive sample of skin commensals such as coagulase-negative staphylococci, *Cutibacterium* species (formerly *Propionibacterium* species) species, or *Corynebacterium* species is not fully clear and often considered a contamination of the sample.

The spectrum of human infections with corynebacteria is broad ranging from community-acquired infections such as conjunctivitis, pharyngitis, genitourinary tract infections, prostatitis, skin and soft-tissue infections, and breast abscess to nosocomial acquired infections such as cerebrospinal fluid shunt infections, pneumonia, intravenous catheter-related bloodstream infections, endocarditis, postsurgical infections, urinary tract infections, and peritoneal dialysis-related peritonitis (4-12). The spectrum of *Corynebacterium* spp. orthopedic infections has not been described so far. In this study, we report the spectrum of *Corynebacterium* spp. isolates of suspected orthopedic infections and compare it with the spectrum of species isolated from patients with suspected blood-stream infections. We discriminated between infections and contaminants based on clinical and

68 microbiological criteria and present antibiotic susceptibility data to describe treatment

69 options.

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METHODS

Orthopedic study population

The orthopedic University Hospital Balgrist in Zurich, Switzerland is a 140-bed orthopedic center. Approximately 5000 orthopedic procedures are performed annually. In this single-center study, we retrospectively identified patients with at least one culture positive sample with *Corynebacterium* spp. derived from synovial fluid, deep tissue/bone, or sonication fluid from removed implants between January 2006 and December 2015. Bacteria labeled as "coryneform bacteria", i.e., aerobic *Actinomyces* spp., *Brevibacterium* spp., *Dermabacter hominis, Lactobacillus* spp., *Cutibacterium* (*Propionibacterium*) spp., and other Gram-positive rods, which were not further characterized, were excluded from our analysis. The latter were found only in single samples in a small amount or in mixed cultures. Cases with lack of clinical data were excluded for our investigation (Figure 1).

Species variation of *Corynebacterium* spp. in suspected orthopedic infections compared to blood-stream infections outside orthopedic wards. We compared the various isolated *Corynebacterium* spp. from orthopedic origins with isolates recovered from blood cultures (from January 2006 to December 2015) in patients with suspected bloodstream infections hospitalized in non-orthopedic wards of the University Hospital of Zurich, Switzerland, with a wide range of medical specialties (e.g., ophthalmology, urology, gynecology, neurosurgery, vascular and heart surgery, dermatology, internal medicine, oncology).

Clinical diagnosis. All samples of the same patient, the same hospitalization period, and the same infection site were considered as one diagnostic set. The number of

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samples with *Corynebacterium* spp., sample type, and the results of antibiotic susceptibility testing (AST) were analyzed using the database of the Institute of Medical Microbiology, University of Zurich in Switzerland. According to the current guidelines by the Infectious Disease Society of America (IDSA) (13), we classified bacteria as a relevant pathogen, when the same species was cultured in ≥ 2 samples and as a contaminant when a species was detected in only one of ≥ 2 samples (2). Cases with only one sample per diagnostic set were excluded for further analysis, as a distinction between infection and contamination was not possible in those cases. Patient's clinical and demographic parameters and medical history including time of diagnoses and follow-up were investigated using the clinical database of the orthopedic hospital and the database of the Infectious Diseases Consultation service of the University Hospital of Zurich. We grouped patients with an infection into two groups as followed: i) monobacterial *Corynebacterium* sp. infection, ii) or as part of a polymicrobial infection (*Corynebacterium* sp., and at least another pathogen in ≥ 2 samples). Clinical parameters of symptoms such as fever, redness, swelling, and presence of sinus tract at infection site were reviewed. Patients with an infection were grouped as associated with joint arthroplasty (PJI) or another orthopedic implant (implant-associated infection), as foot or pressure ulcer with or without osteomyelitis, septic arthritis without foreign material, or deep soft tissue infection associated with surgery. An osteomyelitis was defined when histopathology confirmed acute (presence of neutrophils) or chronic osteomyelitis (presence of bone necrosis or sequester), when bone biopsies showed growth of *Corynebacterium* sp., or when osteomyelitis was assumed with magnet resonance imaging (MRI).

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117 In the control group of blood-stream infections, we diagnosed an infection when
118 either ≥ 2 blood cultures were positive with the same *Corynebacterium* sp., when
119 only 1 blood culture plus a vascular catheter was positive and sepsis criteria were
120 fulfilled.

121 The study was performed in line with the current ethical guidelines and approved by
122 the Institutional Review Board in Zurich, Switzerland (KEK Nr. 2016-00145).

123 **Microbiological methods**

124 Pre-diagnostic and diagnostic processing was done as previously described (14).
125 From 2006 to 2011, Gram-positive rods were identified by an in house standard
126 scheme by means of biochemical (15). From 2012 on, strains were identified using
127 matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-
128 TOF MS) using a Bruker MALDI Biotyper as described elsewhere (16) Reference
129 database V.3.3.2.0 (3995 entries) or later database versions were applied with a
130 species cut-off of 1.7 (16, 17). If no or ambiguous identification was achieved by
131 biochemical characterization or MALDI-TOF MS, respectively, and a Gram-positive
132 rod was isolated in more than one sample or from a normally sterile fluid, the
133 identification was confirmed by 16S rRNA gene sequence analysis (18).
134 *Corynebacterium* spp. that could not be assigned to species level due to high
135 homology of 16S rRNA gene sequences, were identified on genus level as
136 *Corynebacterium* sp. (19).

137 Screening for antimicrobial susceptibility was performed by disc diffusion
138 tests on Mueller-Hinton agar (Becton Dickinson, Cockeysville, MD) supplemented
139 with 5% sheep blood before 2011 and on Mueller-Hinton agar (Becton Dickinson)

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supplemented with defibrinated horse blood and 20 mg/L beta-NAD (MH-F) from 2011 on; zone diameters were interpreted according to CLSI guidelines for staphylococci as closest surrogate for corynebacteria before 2011 (20), according to EUCAST breakpoints for staphylococci from 2011 to 2013 and according to EUCAST guidelines for corynebacteria from 2014 on (21). For this study, zone diameters of the period 2011-2013 were reinterpreted retrospectively according to the latest EUCAST guidelines for corynebacteria (21). MIC testing by Etest was done for relevant *Corynebacterium* isolates and single drugs to confirm disc diffusion tests and for strains with poor growth throughout the study period (data not shown).

Statistical analysis

Categorical data were tested for differences using Fisher's exact or chi-squared tests, as appropriate, whereas continuous variables were tested using Wilcoxon rank sum tests. Two-tailed P-values <0.05 were considered statistically significant.

RESULTS

***Corynebacterium* strains and variation.** We identified 128 *Corynebacterium* sp. isolates in 97 cases at the Orthopedic University Hospital Balgrist between 2006 and 2015 (Figure 1). The median age of all inlcuded patients was 66 years (range, 9-86 years) with a predominance of men (67%), in the patients with an infection, the median age was 54.5 years (range, 25-83 years), 56.3% of them were male. Most commonly, *Corynebacterium tuberculostearicum* (n=26), *Corynebacterium amycolatum* (n=17), *Corynebacterium striatum* (n=13), or *Corynebacterium afermentans* (n=11) were found as the single pathogen in 97 cases with suspected orthopedic infections (Table 1). In 13 cases, identification of *Corynebacterium* to species level was not available. In two cases, two different *Corynebacterium* sp. were cultivated in the same diagnostic set.

For 31 out of 97 cases we could not distinguish between infection and contamination as only one diagnostic sample was sent to microbiological analysis. Among the remaining 66 cases with ≥2 samples, we identified 16 cases (24.2%) with an infection due to *Corynebacterium* sp., in 50 cases only one samples was positive in culture and thus considered a contamination.

Of 66 cases the median number of analyzed samples per case was four (range 2-11); in the cohort of 16 infections, the median was 5 (range 2-8) with a mean positivity of 67.8% (SD ± 28.8%).

Infections were associated with a native (n=1, 6.3%) or prosthetic joint (PJI, n=4, 25%), an orthopedic implant other than joint prosthesis (n=5, 31.3%), a deep foot or pressure ulcer (n=4, 25%), or deep postsurgical soft tissue infection (n=2, 12.5%)

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(Supplementary Table 1). All infections sites were found at the lower extremities (feet n=7, knee n=5, hip n=3, and gluteal n=1). Knee arthroplasty was involved in 75% (n=3) of the PJI cases.

Typical inflammatory signs including redness, pain, or swelling were present in the majority (n=10, 62.5%) of the infections. Among the four cases diagnosed with PJI, all presented as chronic infections with a sinus tract after a prolonged wound healing. Within the four patients with deep ulcer diagnosis, acute osteomyelitis was additionally diagnosed.

Nine out of 16 infections (56.3%) were diagnosed as a polymicrobial infection including the four patients with ulcer diagnosis. In addition to corynebacteria, staphylococci, streptococci, and *Enterobacteriaceae* were recovered most frequently form polymicrobial samples. Monobacterial infections (n=7) were either caused by *C. striatum* (n=3), *C. tuberculostearicum* (n=1), *C. amycolatum* (n=1), *Corynebacterium ureicelerivorans* (n=1), or a *Corynebacterium* sp. (n=1), which could not further be specified even after sequencing of the strain. Supplementary Table 1 summarizes all mono- and polymicrobial infections grouped according to infection diagnosis.

The majority of the infections were diagnosed while already taken antibiotics (n=9). Antibiotic treatment widely differed on the one hand due to different pathogens of the mostly polymicrobial infections but on the other hand due to different antimicrobial susceptibility testing results of isolated *Corynebacterium* spp.

Surgical treatment was debridement (in presence of an implant with retention of the implant) in five, definitive removal of the implant in five, amputation in four, and an exchange of the implant in two cases. Since all PJI presented with a sinus tract as a

200 sign of chronic infection, an aggressive surgical treatment was chosen from the
201 beginning with either a two-stage exchange in two, definitive removal of the
202 prosthesis (girdlestone) in one, and amputation in one patient.

203 The *Corynebacterium* species spectrum in 97 orthopedic cases was different from
204 the spectrum of 70 cases with 86 positive blood culture samples isolated in patients
205 with suspected bloodstream infections. In blood cultures, the diversity of
206 corynebacteria seemed broader with a predominance of *Corynebacterium jeikeum*
207 that was not detected in orthopedic samples, and with significantly less *C. striatum*
208 and *C. tuberculostearicum* compared to orthopedic cases (Table 1).

209 **AST**. Susceptibility testing was done in 62 out of 128 (48.4%) orthopedic
210 *Corynebacterium* isolates and 64 out of 70 (91.4%) blood culture isolates (Table 2).
211 Percentage of susceptible orthopedic *Corynebacterium* isolates were 72% for
212 gentamicin, 28% for penicillin, 81% for tetracycline, 100% for vancomycin, 44% for
213 ciprofloxacin, 6% for clindamycin, 100% for linezolid and 82% for rifampin using
214 EUCAST breakpoints (2011-2015). Rates of susceptibility of corynebacteria isolated
215 from orthopedic samples and of isolates from blood cultures were comparable (Table
216 2, data of rates are not shown). Supplementary Table 2 shows susceptibility testing
217 results of the four most commonly isolated *Corynebacterium* spp. in orthopedic
218 patients. All isolates were susceptible to vancomycin and linezolid. In contrast,
219 penicillin resistance was observed in 78% of *C. tuberculostearicum*, in 80% of *C.*
220 *amycolatum*, in 100% of *C. striatum*, and in 62% of *C. afermentans*. Tetracycline,
221 ciprofloxacin, clindamycin, rifampin, and gentamicin showed variable frequencies of
222 resistance among different species. Susceptibility testing of corynebacteria isolated
223 between 2006 and 2010 was done according to CLSI recommendations. Rates of

susceptible isolates for gentamicin and vancomycin were similar when results of the years 2006 to 2010 (CLSI criteria) and of the years 2011 to 2015 (EUCAST criteria) were compared. For penicillin and tetracycline, a significantly lower rate of susceptibility was observed using EUCAST interpretive criteria (2011-2015) compared to CLSI ($p=0.005$, $p=0.04$, respectively) (see Table 2).

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DISCUSSION

Our study identified a provenorthopedic infection due to *Corynebacterium* sp. in only 24.2% of the cases in whom a *Corynebacterium* sp. had been isolated over a period of 10 years. The same phenomena was observed in patients with positive blood cultures with a proved infection in only 24.3%. We found that implant-associated infections and ulcers with or without osteomyelitis were the most common diagnosis in orthopedic patients as previously described (22).

The *Corynebacterium* spp. isolated from orthopedic samples differed from the species spectrum isolated from blood culture samples. We found 26 orthopedic cases with *C. tuberculostearicum.* This typical inhabitant of the skin is often described in association with intravascular catheter associated infection (12) but rarely with orthopaedic infections (11). *C. striatum* was found more frequently in orthopedic samples as compared to blood culture samples (13.4% vs 2.9%) and counted for three monomicrobial infections (two implant-associated infections and one septic arthritis). In the literature, *C. striatum* is associated with foreign-body-associated infections, infective endocarditis, pulmonary infections, septic arthritis, and ventilator tubes in hospital settings (12, 23, 24). *C. jeikeium* was recoverd in 20% of our *Corynebacterium* positive blood cultures but not in any of the orthopedic samples. *C. jeikeum* has been described as cause of endocarditis, bacteremia, cerebrospinal fluid shunt infections, peritoneal dialysis peritonitis and rarely as cause of PJI (11, 25, 26). Biochemical characteristics and cell envelope structure are key factors for the adaption to a certain habitat or body site predilection. Lipophilic corynebacteria are part of the human skin flora but can invade deep tissue after surgery for example. In contrast, we also described invasive infections with non-

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lipophilic corynebacteria (*C. aurimucosum, C. simulans,* and *C. striatum*). The pathogenesis of these infections is not yet explained.

Identification of corynebacteria to species level is challenging and often requires 16S rRNA and *rpoB* gene sequencing and/or nowadays MALDI-TOF MS analysis in addition to morphological and biochemical characterization (16-18, 27). Before 2012, the identification of corynebacteria to species level by biochemical identification followed by 16S rRNA gene sequencing was restricted in our laboratory to relevant Gram-positive rods isolates. In 2012, our laboratory introduced MALDI-TOF MS for the identification of bacteria; rapid and reliable identification became available for most Gram-positive rods. However, we do not exclude that we missed infections before the application of MALDI-TOF MS.

There are no clinical data available on how to best treat *Corynebacterium* sp. implant-associated infections. AST has to be performed on all *Corynebacterium* isolates causing orthopedic infections if antibiotics other than vancomycin are given (28-30). We found that only 20 to 38% of the isolated *C. tuberculostearicum C. amycolatum*, and *C. afermentans* were susceptible to penicillin and none of the *C. striatum*. Clindamycin, ciprofloxacin, gentamicin, rifampin, and tetracycline were not regularly effective against these corynebacteria making vancomycin the only valid empiric treatment until susceptibility testings are performed. Variable resistances were observed in different *Corynebacterium* spp. as already shown in the study by Reddy et al. who observed a high frequency of penicillin resistant strains (>50%), as well as erythromycin, clindamycin and gentamicin resistant strains (31). Further studies are needed to investigate combination antibiotic treatment , e.g. a quinolone

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276 plus rifampicin, for treatment of implant-associated infections as is currently routinely
277 used for treating other Gram-positive infections such as staphylococci (1).

278 Guidelines on how to perform and interpret AST of corynebacteria are sparse.
279 CLSI provides clinical breakpoints (CBP) for broth microdilution of corynebacteria
280 since 2006; EUCAST published CBPs for microdilution and disk diffusion methods in
281 2014. CLSI and EUCAST both defined CBPs for all *Corynebacterium* spp. (for MIC
282 and/or zone diameter) based on small numbers of each *Corynebacterium* sp. or
283 even inferred breakpoints from staphylococcal CBP (i.e. CLSI criteria for gentamicin,
284 vancomycin and tetracycline); in particular, EUCAST defined clinical breakpoints
285 without defining epidemiological cutoffs (ECOFFs) separating the wild type
286 population from the strains with a resistance against a given antibiotic
287 (http://www.eucast.org/clinical_breakpoints/, update 03/2017). The breakpoints of
288 CLSI and EUCAST and as a consequence the rates of susceptible and resistant
289 isolates may therefore differ significantly. From 2006 to 2010, we used CLSI
290 staphylococcal breakpoints for zone diameters due to the lack of breakpoints specific
291 for corynebacteria. Penicillin susceptibility was observed in 65% of the isolates. In
292 contrast, applying the EUCAST corynebacteria breakpoints resulted in only 28%
293 susceptible isolates. This shift was mainly caused by a change of the antibiotic discs
294 used switching from 10 units penicillin (CLSI) previously to currently 1 unit penicillin
295 (EUCAST). It will be necessary to collect more data on corynebacteria so that
296 breakpoints can be defined for each species individually based on the distribution of
297 zone diameters and MICs of strains without acquired resistance.

298 Our observation that *Corynebacterium* sp. rarely belongs to an infection when
299 isolated on an orthopedic ward is only a single hospital report and may not represent

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experiences at other sites. However, it is also mentioned in the report of Cazanave *et al.* that *Corynebacterium* spp. are only occasional causes of PJI as a typical orthopedic infection (11). The strength of our retrospective analysis is the long observation period of 10 years in a large orthopedic center. We might have missed some infections due to our strict definition of at least two positive diagnostic samples. In patients with foot ulcers, often only one bone biopsy was taken for microbiology and histopathology and thus the numbers we present are most probable an underestimation. Nevertheless, our study highlights that isolation of *Corynebacterium* spp. in orthopedic patients rarely indicates an infection even when isolated in more than one sample. However when diagnosed, *Corynebacterium* spp., infections are often polymicrobial. It is crucial to test antimicrobial susceptibility of clinically relevant *Corynebacterium* spp. since resistance varies between different species. It remains to be investigated under which conditions corynebacteria change from a commensal to an invasive pathogen.

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Acknowledgment

Yvonne Achermann was supported by the academic career program “filling the gap” of the Medical Faculty of the University of Zurich. We thank Thomas Klein and the technicians of the Institute of Medical Microbiology of the University of Zurich for expert help and assistance.

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421

TABLES AND FIGURES

Table 1. Variation of *Corynebacterium* spp. strains isolated in 97 patients with suspected orthopedic infections (thereof 16 individuals had a proofed infection) as compared to *Corynebacterium* spp. strains recovered from blood cultures from 70 patients with suspected blood-stream infections (of these 17 had a proofed infection).

Microbiological characteristics	**No. (%) of patients with positive orthopedic isolates ***	**No. (%) of patients with positive blood cultures**	**P-value**	**No. of orthopedic infections**	**No. of blood-stream infections**
Total	**N=97**	**N=70**		**N=16**	**N=17**
C. accolens	1 (1.0)	1 (1.4)	1.0	0	1
C. afermentans	11 (11.4)	8 (11.4)	1.0	0	0
C. amycolatum	17 (17.5)	11 (15.7)	0.8	3	7
C. aurimucosum	2 (2.1)	3 (4.3)	1.0	1	0
C. diphtheriae biovar *mitis*	1 (1.0)	0 (0)		1	0
C. glucuronolyticum	1 (1.0)	1 (1.4)		0	0
C. imitans	0	2 (2.9)		0	0
C. jeikeium	0	14 (20.0)	0.0001	0	7

Microbiological characteristics	**No. (%) of patients with positive orthopedic isolates ***	**No. (%) of patients with positive blood cultures**	**P-value**	**No. of orthopedic infections**	**No. of blood-stream infections**
Total	**N=97**	**N=70**		**N=16**	**N=17**
C. macginleyi	0	1 (1.4)		0	0
C. minutissimum	1 (1.0)	4 (5.7)	0.162	0	1
C. mucifaciens	1 (1.0)	4 (5.7)		0	0
C. pseudodiphtheriticum	1 (1.0)	0 (0)		0	0
C. propinquum	0	1 (1.4)		0	0
C. simulans	5 (5.2))	2 (2.9)	0.700	1	0
C. striatum	13 (13.4)	2 (2.9)	0.026	3	1
C. tuberculostearicum	26 (26.8)	3 (4.3)	0.001	3	0
C. ureicelerivorans	2 (2.1)	0 (0)		1	0
Corynebacterium sp.	13 (13.4)	13 (18.6)		1	0
Polymicrobial **	2 (2.06)	0		2	0

426 * Most commonly isolated orthopedic strain spp. are labelled in bold, ** Isolation of two different *Corynbacterium* spp. strains (one

427 case with *C. aurimucosum/C. amycolatum*, one with *C. auris/C. aurimucosum*)

428 **Table 2.** Antibiotic susceptibility testing (AST) of *Corynebacterium* spp. isolated between 2006 and 2015.

Species	Years	CBP[1]	Sample origin	Susceptible isolates (%)								
				ERY[2]	GEN	PEN	TET	VAN	CIP	CLI	LZD	RIF
Corynebacterium spp. (n=26)	2006-2010	CLSI	Orthopedic	35	85	65	100	100	nd	nd	nd	nd
Corynebacterium spp. (n=36)	2011-2015	EUCAST	Orthopedic	nd	72	28	81	100	44	6	100[3]	82[3]
Corynebacterium spp. (n=36)	2006-2010	CLSI	Blood culture	22	64	47	92	100	nd	nd	nd	nd
Corynebacterium spp. (n=28)	2011-2015	EUCAST	Blood culture	nd	61	29	78	100	29	19	100[4]	88[4]

429 [1] AST was performed by disc diffusion. Clinical breakpoints (CBP) from CLSI (20) were applied from 2006-2010 and EUCAST CBP
430 from 2011-2015 (21).

431 [2] ERY, erythromycin; GEN, gentamicin; PEN, penicillin; TET, tetracycline; VAN, vancomycin; CIP, ciprofloxacin; CLI, clindamycin;
432 LZD, linezolid; RIF, rifampin.

[3] DST data available for LZD and RIF for n=12 and n=17 isolates, respectively.

[4] DST data available for LZD and RIF for n=12 and n=17 isolates, respectively.

FIGURE LEGENDS

Figure 1. Flowchart of 97cases and 128 positive samples in whom *Corynebacterium* spp. were isolated describing variation of different species in suspected orthopedic infections, in analysis of antibiotic susceptibility testing (AST), or clinical characteristics of infections